REPLACEMENT SPECIFICATION PAGES

P0136

METHOD FOR TREATMENT OF NEURODEGENERATIVE DISEASES AND EFFECTS OF AGING

BACKGROUND

a. Field of the Invention

The present invention relates generally to methods for the treatment of neurological conditions, and, more particularly, to a method for alleviating/controlling symptoms associated with neurodegeneration and similar conditions stemming from multiple sclerosis, aging, autoimmune diseases and other causes, by administration of compositions which induce an increased presence of histamine H2 and cyclic AMP in the body.

b. Related Art

Neurodegenerative conditions, which include diseases of autoimmunity, strike an increasing number of individuals each year, and for many of these conditions conventional treatments offer little in the way of true relief. In some instances, the neurodegenerative conditions are more or less specifically associated with a particular disease, such as multiple sclerosis, while in other instances the conditions are associated more generally with aging or some other condition or process of the body, such as a genetic disorder or an autoimmune disease, fibromyalgia, for example. As a group, however, these conditions are characterized by weakness and impaired physical functions, and, sometimes, impaired mental functions as well. Debilitation is often progressive, and, as stated, conventional treatments and therapies have been limited in their success.

For purposes of illustration the invention will be described below largely in the context of multiple sclerosis, which is a condition to which the invention has particular applicability; however, it will be understood that the present invention is applicable to neurodegenerative conditions, including autoimmune diseases, fibromyalgia, having any of a variety of sources, therefore it is not limited in scope to the treatment of multiple sclerosis alone.

SUMMARY OF THE INVENTION

The present invention addresses the problems cited above, and is a method for treatment of neurodegenerative disease conditions stemming from multiple sclerosis, aging, autoimmune diseases, and fibromyalgia, the method broadly comprising the step of administering to a patient a compound effective to increase neuronal metabolism of histamine to a histamine H_2-agonist, in an amount sufficient to stimulate production of cyclic AMP at a level which is sufficient to maintain myelin against undergoing self-degeneration.

The method may further comprise the step of selecting the compound from the group consisting of histamine N-methyltransferase, monoamine oxidase-A, monoamine oxidase-A agonists and histamine H_3 antagonists.

The compound may comprise histamine N-methyltransferase, and the step of administering the compound may comprise administering histamine N-methyltransferase to the patient so as to increase neuronal metabolism of histamine to tele-methylhistamine. The step of administering histamine N-methyltransferase may comprise administering isolated histamine N-methyltransferase by injection.

In another embodiment, the compound may be monoamine oxidase-A, and the step of administering the compound may comprise administering monoamine oxidase-A to the patient so as to increase neuronal metabolism of tele-methylhistamine to an H_2 receptor agonist such as 4-methylhistamine.

In another embodiment, the compound may be a monoamine oxidase-A agonist, and the step of administering the compound may comprise administering the monoamine oxidase-A agonist to the patient so as to increase neuronal metabolism of tele-methylhistamine to an H_2 agonist such as 4-methylhistamine. The monoamine oxidase-A agonist may be reserpine, and the step of administering the monoamine oxidase-A agonist may comprise administering reserpine by slow-release transdermal dose. Alternatively, the step of administering the monoamine oxidase-A agonist may comprise administering reserpine by injection, preferably in the range from about 1-10 mg/kg S.C. per day.

In another embodiment, the compound may be a histamine H_3 antagonist, and the step of administering the compound may comprise administering a histamine H_3 antagonist to the patient so as to inhibit neuronal metabolism of tele-methylhistamine to an H_3 agonist such as

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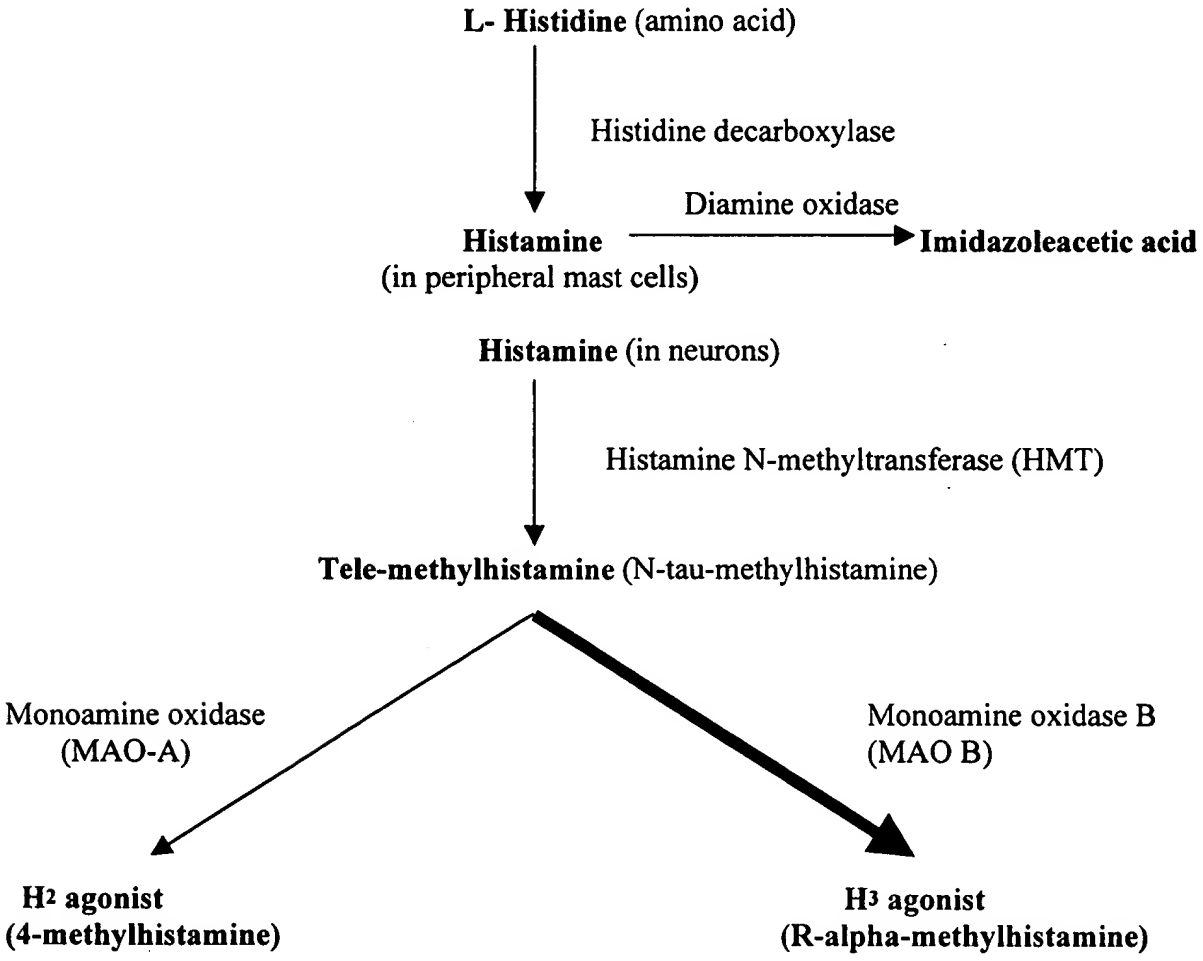
R-alpha-methylhistamine and thereby increase neuronal metabolism of tele-methylhistamine to an H_2 agonist such as 4-methylhistamine. The histamine H_3 antagonist may be thioperamide maleate.

These and other features and advantages of the present invention will be apparent from a reading of the following detailed description.

It is hypothesized from the above data (indicating that those individuals having the lowest histamine levels demonstrated the most improvement) that the underlying problem is not in the supply of histamine to the neurons, but instead may be in the ability of the neurons to effectively metabolize histamine into histamine H_2.

To illustrate this, Table C shows the sequential steps in the production and metabolism of histamine to yield histamine H_2.

TABLE C



As can be seen, histamine is synthesized initially from L-histidine by the enzyme histidine decarboxylase. The histamine is stored in mast cells in the blood and most tissues in the body. Histamine that is released from mast cells results in an allergic response.

Histamine outside the brain is converted to imidazoleacetic acid by diamine oxidase (histaminase) (Ganong, Review of Medical Physiology, 6th Ed., 1973, pp.185-86). Histamine in the brain is mostly methylated by histamine N-methyltransferase to form tele-methylhistamine. Monoamine oxidase metabolizes the tele-methylhistamine further into R-alpha-methylhistamine (an H_3 agonist) and 4-methylhistamine (an H_2 agonist) (Oishi, "Turnover of brain histamine and its changes by various drugs", Nippon Yakurigaku Zasshi, Nov 1988, 92:271-81).

Research shows that the histamine level in the cerebral spinal fluid of MS patients is 60% higher than that of controls, while the activity of histamine N-methyltransferase (HMT) is significantly lower than that of controls, tending to confirm that MS patients have an impaired histamine metabolism (Tuomisto et al, "Histamine and histamine-N-mehtyltransferase in the CSF of patients with multiple sclerosis", 1983). This is congruent with the findings from the study referred to above (which used an H_2 agonist and a phosphodiesterase inhibitor), in which 100% of the study subjects in the placebo group showed an overall increase in their whole blood histamine levels in the first 30 days. This elevated level of whole blood histamine persisted for the entire 90-day study in 80% of the placebo subjects (who did not receive the histamine H_2 agonist), and was probably due to the skin irritation caused by the citric acid placebo and transdermal patch. 95% of the verum group also experienced an elevation in their whole blood histamine in the first 30 days, but unlike the placebo group, for 80% of those showing initially elevated histamine levels, it was followed by a decrease in whole blood histamine. Those patients whose whole blood histamine level increased and then decreased the most significantly, experienced the most improvements in the symptoms tested.

These phenomena may be explained in that an H_2 agonist, such as that administered in the study, may decrease the histamine level by stimulating the Histamine N-methyltransferase activity. For example, in a study by Maroi et al ("Effect of reserpine on histamine metabolism in the mouse brain", Mar 1991, 256:967-72), reserpine, which can stimulate H_2 receptors, inhibited the histamine increase induced by a histamine N-methyltransferase inhibitor, while having no significant affect on a histidine decarboxylase inhibitor. Consequently, it is believed that the histamine H_2 agonist administered during the study caused the HMT system to increase HMT activity and thereby increase the metabolism of histamine, resulting in the observed decrease in whole blood histamine levels.

Therefore, based on the results of the 29-patient study and other research, it is postulated that an altered histamine metabolism is associated with MS and related neurodegenerative conditions, resulting in a decrease in the turnover of histamine, and therefore lower histamine H_2 levels, leading ultimately to inadequate cAMP production. This view is consistent with the results of the Tuomisto study referenced above, which showed that the histamine level in MS patients was 60% higher than in non-MS patients while the activity of the enzyme, HMT, was significantly lower than in controls.

The study results set forth above also suggest that the problem with the metabolism of histamine in MS patients probably does not lie in the histidine decarboxylase enzyme activity, but rather in the activity of HMT or the monoamine oxidase enzymes, since it is clear the MS patients in the study were capable of producing whole blood histamine. MS patients are therefore apparently able to produce histamine from L-histidine via the enzymatic activity of histidine decarboxylase, but further metabolism of histamine in the neurons is impaired. This impaired neuron histamine metabolism may be due to either inadequate HMT activity or impaired MAO activity, or possibly both.

i. HMT Activity

Inadequate HMT activity may be the result of impaired synthesis of the enzyme. Based on this etiology, HMT levels may be beneficially supplemented by administration of the compound itself, i.e., by injections or other administration of the HMT enzyme. For example, HMT isolated as described in U.S. Patent No. 4,769,322 (to Eli Lilly & Co.) may be administered parenterally, such as by intramuscular or subcutaneous injections, and possibly via transdermal application or oral administration.

ii. MAO activity

As explained above, reduced metabolism of histamine may also be the result of impaired monoamine oxidase (MAO) activity.

Inadequate activity of monoamine oxidase-A and/or monoamine oxidase-B can result in an accumulation of tele-methylhistamine, which in turn causes an inhibition of HMT and an accumulation of histamine. As is indicated by the bold arrow in Table C, tele-methylhistamine is primarily metabolized via monoamine oxidase B (MAO-B) into an H_3 agonist (R-alpha-methylhistamine) (Elsworth et al, "Tele-methylhistamine is a specific MAO-B substrate in man", Psychopharmacology, 1980, 69:287-90). The release of histamine is regulated by H_3 autoreceptors (Prast et al., "In vivo modulation of histamine release by autoreceptors and muscarinic acetylcholine receptors in the rat anterior hypothalamus", Naunyn Schmiedebergs Arch Pharmacol, Dec 1994, 350:599-604). Tele-methylhistamine is metabolized by a second path into an H_2 agonist (4-methylhistamine), via monoamine oxidase A (MAO-A). Hence, the relative amounts of H_2 and H_3 agonists produced depends primarily on the relative activity of the MAO-A and MAO-B metabolic paths.

The MAO-A:MAO-B activity ratio is genetically encoded on the X chromosome (Garpenstrand et al, "Platelet monoamine oxidase activity is related to MAOB intron 13 genotyp", J. Neural Transm, 2000, 107:523-30). Interestingly, MS is more predominant in females than males. Estrogen and aging also selectively affect the synthesis of MAO-A. Estrogen decreases MAO-A activity in the hypothalamus, but does not affect the activity of MAO-B (Edelstein & Breakefield, "Monamine oxidases A and B are differentially regulated by glucocorticoids and "aging" in human skin fibroblasts", Cell Mol Neurobiol, Jun 1986, 6:121-50). The MAO-A:MAO-B activity ratios also decrease in all regions of the brain during maturational development in rats, and research has shown that the ontogenetic development of MAO-A and MAO-B in the human brain is parallel to that observed in the rodent brain (Strolin et al, "Developmental aspects of the monoamine-degrading enzyme monoamine oxidase", Dev Pharmacol Ther, 1992, 18:191-200).

As the MAO-A:MAO-B activity ratio decreases, metabolism of tele-methylhistamine via MAO-B becomes more dominant and MAO-A activity is inhibited. Elevated activity of MAO-B is associated with neurodegenerative disorders such as Parkinson and Alzheimer's diseases

(Carlo et al, "Monoamine oxidase B expression is selectively regulated by dexamethasone in cultured rat astrocytes", Brain Res, Mar 1996, 4:175-83). Inhibition of MAO-A activity also results in a significant decrease in the responsiveness of the noradrenergic cyclic AMP generating system (Mishra et al, "Effect of selective monamine oxidase inhibition by clorgyline and deprenyl on the norepinephrine receptor-couple adenylate cyclase system in rat cortex", Psychopharmacology, 1983, 81:220-3). The H_2 agonist (4-methylhistamine) is the metabolite of tele-methylhistamine via MAO-A and is a potent stimulator of cyclic AMP synthesis. Thus, a decrease in MAO-A activity results in decreased H_2 receptor stimulation, which results in decreased cAMP production. As stated above, deficient cAMP production is believed to be directly involved in demyelination in MS and similar neurodegenerative conditions.

Other contributors to MAO-A inhibition may include stress. It is known that exacerbations or worsening of symptoms in MS patients are often triggered by stress. Research shows that stress stimulates the release of endogenous MAO-A inhibitors (Glover, "Function of endogenous monoamine oxidase inhibitors (tribulin), J Neural Transm Suppl, 1998, 52:307-13). Stress may thus be an added factor in the endogenous inhibition of an already deficient activity of MAO-A.

Lipid peroxidation is also known to inhibit the monoamine oxidase system (Medvedev et al, "The role of lipid peroxidation in the possible involvement of membrane-bound monoamine oxidases in gamma-aminobutyric acid and glucosamine deamination in rat brain. Focus on chemical pathogenesis of experimental audiogenic epilepsy", Mol Chem Neuropathol, Feb-Apr 1992, 16:187-201). MS patients have low levels of copper and zinc as discussed earlier, which debilitates the Cu-Zn-superoxide dimutase enzyme. Inhibition of this enzyme results in an increase in superoxide and nitric oxide which results in the formation of peroxinitrites, a free radical that leads to myelin destruction in MS (Johnson, "The possible role of gradual accumulation of copper, cadmium, lead and iron and gradual depletion of zinc, magnesium, selenium, vitamins B2, B6, D, and E and essential fatty acids in multiple sclerosis", Sep 2000, 55:239-41). Deficient levels of copper in MS patients also interferes with the synthesis of the monoamine oxidases themselves, because they are copper-containing enzymes.

A decrease in MAO-A activity caused by one or more of the mechanisms described above will decrease the MAO-A:MAO-B ratio. The resulting disproportion of the MAO-

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A:MAO-B ratio results in a parallel disproportion in the production ratio of the H_2 agonist (4-methylhistamine) to

the H_3 agonist (R-alpha-methylhistamine). Increased production of the H_3 agonist (R-alpha-methylhistamine) then further inhibits MAO-A activity, compounding the H_2 deficiency.

Inhibition of MAO-B activity would increase the MAO-A:MAO-B activity ratio, thereby increasing histamine H_2 levels. An H_3 antagonist such as thioperamide maleate inhibits MAO-B (Sakurai et al, "Effects of the histamine H_3 agonist (R)-alpha-methylhistamine and the antagonist thioperamide in vitro on monoamine oxidase activity in the rat brain", Exp Clin Pharmacol, Nov 1995, 17C:46-50). It may therefore be beneficial to administer an H_3 antagonist such a thioperamide maleate in order to increase the MAO-A:MAO-B activity ratio. Thioperamide maleate is available in suitable form from VWR Scientific Products, a company of the Merck Group.

It may also be beneficial to administer MAO-A agonists such as reserpine. Reserpine oxidizes serotonin and is therefore similar in action to MAO-A, since MAO-A also oxidizes serotonin (Benedetti & Keane, "Differential changes in monoamine oxidase A and B activity in the aging rat brain", J Neurochem, Nov 1980, 35:1026-32). Injecting reserpine in dosages of about 1-10 mg/kg S.C. per day, or using a slow release transdermal dose, will be sufficient in most instances to increase the metabolism of tele-methylhistamine to a histamine H_2 agonist, e.g., 4-methylhistamine, resulting in adequate H_2 receptor stimulation. Reserpine is available in suitable form from VWR Scientific Products.

It is to be recognized that various alterations, modifications, and/or additions may be introduced into the constructions and arrangements of parts described above without departing from the spirit or ambit of the present invention.